REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and these comments, along with a Rule 132 declaration, discussed below, which is concurrently filed.

I. Specification Amendment

For those figures that depict sequences, the specification has been amended to include sequence identifiers in the "Brief Description of the Drawings" section. Additionally, the specification has been amended to include trademark symbols, where appropriate.

II. Status of Claims

Claims 137-139 are pending. Claims 138 and 139 have been amended such that they no longer depend from a canceled claim.

III. Rejection Under 35 U.S.C. § 112, first paragraph (written description)

Claims 137-139 are rejected on the grounds that they allegedly do not have written-description support in the original specification. In particular, the Examiner maintains that "the written support for the particularities of the ranges and modifications recited in claim 137...are not readily apparent in the specification as filed." Office Action at 3 (emphasis in original).

Applicants respectfully disagree. Support for the heavy chain sequence as claimed is found in the specification, *inter alia*, at pages 35-36 that describe the 474 amino acid heavy chain antibody sequence of SEQ ID NO:140. At page 35, moreover, the specification identifies a boundary, delineating the signal sequence and the variable region of the heavy chain of SEQ ID NO:140, that is between serine (S) at position 26 and glutamine (Q) at position 27. Thus, there is written description in the specification that the mature heavy chain of the claimed antibody begins at glutamine (Q) at position 27 and continues to the end of the heavy chain, which is lysine (K) at amino acid position 474.

Support for the light chain sequence, as claimed, is found in the specification, *inter alia*, at pages 36-37, as amended on February 16, 2009, which describe the 235 amino acid light chain antibody sequence of SEQ ID NO:142. Additionally, the cited portion of the specification describes that the boundary between the signal sequence and the variable region of the light chain of SEQ ID NO:142 is located between cytosine [*sic*-cysteine] (C) at position 22 and alanine (A) at position 23 (see page 37). Thus, the mature light chain of the claimed antibody begins at alanine (A) at position 23 and continues to the end of the light chain, which is cysteine (C) at amino acid position 235.

The Examiner states that "the written description of ranges per se as well as the modifications...are not readily apparent in the specification as-filed." Office Action at 3. Applicants are uncertain what the Examiner means by "modifications," as the claims refer to specific portions of SEQ ID NOs: 140 and 142 (*i.e.*, amino acids 27 to 474 of SEQ ID NO: 140 and amino acids 23 to 235 of SEQ ID NO: 142). There is no mention of a modification or mutation, therefore.

The claimed antibody, also referred to as "4D11G4PE" in the specification, contains two point mutations in the IgG4 heavy chain constant region of the antibody. The serine at position 228 is substituted with proline (S228P) and the leucine at position 235 is substituted with glutamate (L235E). These "position" denotations relate to the EU index elaborated in Kabat *et al.* See specification at page 30, first and third paragraphs. If the Examiner is referring to these two substitutions, then Applicants would note that these mutations are present in the sequence of SEQ ID NO:140 and, hence, are described in the application as filed. By the same token, these mutations are not recited, *per se*, but rather are inherent aspects of SEQ ID NO:140, which is both recited in the claims and amply described in the specification.

IV. Rejection Under 35 U.S.C. § 103(a)

Claims 137-139 are rejected over WO 02/088186 to Mikayama *et al.* ("Mikayama PCT") or U.S. Patent No. 7,193,064 to Mikayama *et al.* ("Mikayama") in view of U.S. Patent No. 6,998,124 to Erickson-Miller *et al.* ("Erickson-Miller"), U.S. Patent No. 6,936,698 to Taylor ("Taylor"), and U.S. Patent No. 6,376,653 to Holmes *et al.* ("Holmes"). Office Action at 4 and 7. Applicants respectfully traverse rejection.

The Examiner alleges that Mikayama PCT and Mikayama disclose the 4D11 anti-CD40 antibody, pharmaceutical compositions containing the antibody and methods of inhibiting immunological graft rejection. Office Action at 4 and 7. The Examiner acknowledges that neither Mikayama PCT nor Mikayama suggests modifying the 4D11 antibody, thereby to arrive at the presently claimed antibody. *Id.* Rather, the Examiner alleges that Erickson-Miller, Taylor, and Holmes "provide for modifying therapeutic antibodies containing point mutations S228P and L235E in the IgG4 constant region." Office Action at 5 and 8. That is, the Examiner concludes that one of ordinary skill would have been motivated to produce the claimed invention with a reasonable expectation of success:

> One of ordinary skill in the art at the time the invention was made would have been motivated to provide modified IgG4 immunoglobulin variants of the 4D11 anti-CD40 antibody, given the teachings of the prior art of providing IgG4 modifications to therapeutic antibodies of interest in order to increase half-life or to modify effector function of therapeutic antibodies, as taught by the secondary references....From the teaching of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Id. at 5.

Without acquiescing to this perspective on the prior art, Applicants submit that the claimed antibody displays activity, both *in vitro* and *in vivo*, that would have been wholly unexpected in the art, thus vindicating the patentability of the present claims. Elaborating on this point below, Applicants also make of record the accompanying "Declaration under 37 C.F.R. § 1.132 by Dr. Nobuaki Takahashi" ("Takahashi Declaration"). Dr. Takahashi is a named co-inventor on this application. Applicants were unable to obtain Dr. Takahashi's

signature of the declaration prior to filing of the present reply. However, Applicants will submit an executed version of the Takahashi Declaration shortly.

As noted above, the antibody of the claimed invention is designated "4D11G4PE" in Applicants' specification, *e.g.*, on page 35, line 7 from the bottom, and is a mutant of an anti-CD40 antagonistic antibody, designated "4D11," which is described in Mikayama PCT and Mikayama. See the specification, *e.g.*, in the initial two paragraphs on page 5, and also the Takahashi Declaration at ¶ 5.

The 4D11G4PE antibody is an antagonistic anti-CD40 antibody, containing the variable regions of the 4D11 antibody and the constant region of the human IgG4 subclass of antibodies. Relative to 4D11, moreover, the antibody of Applicants' invention contains two amino-acid substitutions in the constant region of the heavy chain.

More specifically, the 4D11G4PE antibody contains two amino acid substitutions at positions S228P and L235E, as indicated by the EU index of Kabat *et al.*, a standard antibody notation system. "S228P" and "L235E" indicate that the serine amino acid at Kabat position 228 was substituted for the amino acid proline and that the leucine amino acid at Kabat position 235 was substituted for the amino acid glutamic acid. The mature heavy and light chains of the 4D11G4PE antibody in the captioned application correspond to amino acids 27 to 474 of SEQ ID NO: 140 and amino acids 23 to 235 of SEQ ID NO: 142, respectively. See Takahashi Declaration at ¶ 7.

By way of some background, CD40 is an antigen that is expressed on B cells and dendritic cells. CD40 interacts with a ligand, CD40L, which is expressed on CD4+T cells. Dendritic cells are activated when CD40 expressed on dendritic cells interacts with CD40L on CD4+T cells. The activation of dendritic cells enhances the expression of auxiliary stimulants, such as CD80 and CD86, and the production of IL-12, which results in induction of cellular immunity by cytotoxic T lymphocytes. Furthermore, when CD40 on B cells interacts with CD40L on CD4+ T cells, B cells grow and differentiate, and antibody production by the B cells is enhanced, resulting in induction of humoral immunity.

An antagonistic anti-CD40 antibody binds to CD40 on B cells and dendritic cells, respectively, to block the interaction between CD40 and CD40L on CD4+ T cells, which in turn inhibits the induction of cellular immunity and humoral immunity. Such an antibody is expected to be useful as a suppressor of rejection, following organ transplantation, or as a drug for treating autoimmune disease. See Takahashi Declaration at ¶ 9.

Yet, when an antibody that recognizes antigens on cells involved in immune responses, such as B cells and dendritic cells, binds to an antigen on such cells, then the Fc region of the antibody interacts with Fc receptors presented by other cells, which induces signals for an immune response in some cases. See Takahashi Declaration at ¶ 10.

Therefore, when an antibody such as an antagonistic anti-CD40 antibody is used to suppress rejection after organ transplantation or to treat autoimmune disease, "it is important that anti-CD40 antagonistic antibodies have no activity to induce signals by their *in vivo* crosslinking via Fc receptors, even if the ADCC activity cannot be detected." Specification at page 27, last full sentence (emphasis added). This is so because, if such antibodies "induce an agonistic activity due to some effect after they are administered to patients, however weak [the activity] may be, [then] the symptoms may worsen in contrast to the desired therapeutic effect." *Id.* at page 28, second full sentence (emphasis and bracketing added). See also the Takahashi Declaration at ¶ 10.

Accordingly, for an antagonistic anti-CD40 antibody it is very important to avoid the induction of CD40 signals (*i.e.*, agonistic activity) brought about by the crosslinking of the antibody via Fc receptors *in vivo*. See Takahashi Declaration at ¶ 11. The claimed antibody, 4D11G4PE, does not exhibit agonistic activity *in vitro* or *in vivo*. Thus, Example 15 and Figure 16 of the captioned application demonstrate that 4D11G4PE does not enhance production of IL-12, an indicator of agonistic activity *in vivo*. See the Takahashi Declaration at ¶ 12. This lack of agonistic activity *in vivo* is critical to the use of an anti-CD40 antibody in the prevention of transplant rejection or as a therapy for autoimmune disease. *Id.*

Erickson-Miller, Taylor, and Holmes describe antibodies that recognize targets other than CD40 but that contain the S228P and L235E mutations in the heavy chain constant

region. These three references state that the S228P and L235E mutations result in reduced effector function, but none even hints at how the mutations of the heavy chain constant region might effect *in vivo* agonistic activity by virtue of the described crosslinking of the antibody to an Fc receptor. See Erickson-Miller at col. 11, ll. 48-52, Taylor at col. 6, ll. 60-66, and Holmes at col. 10, ll. 66 – col. 11, ll. 5.

With no basis for expecting that the same mutations would not have agonistic activity *in vivo* due to such crosslinking, the skilled artisan could not have predicted that an anti-CD40 antibody with these mutations would lack agonistic activity *in vivo*. As Dr. Takahashi attests,

> ... a knowledgeable person, informed by the disclosures of Erickson-Miller, Holmes and Taylor, could not have reasonably predicted whether combining the human IgG4 constant region, with the S228P and L235E mutations and the variable region from the 4D11 antibody would yield an anti-CD40 antibody that exhibited antagonistic activity *in vitro* and, more importantly, *in vivo*.

Takahashi Declaration at ¶ 17.

In this regard Dr. Takahashi discusses a study by Reddy *et al.*, *J. Immunology* 164: 1925-33 (2000), of an anti-CD4 antibody, "clenoliximab," which has the same S228P and L235E mutations as the antibody of Applicants' claimed invention. As Dr. Takahashi explains, Reddy *et al.* documented that clenoliximab loses the binding activity to Fc receptor *in vitro* (Figure 4B). Clenoliximab induces strong CD4 modulation *in vivo*, however, due to the crosslinking of the antibody on CD4 via Fc receptors. Takahashi Declaration at ¶ 18.

With respect to Fc receptor activation, therefore, an antibody disclosed in the art that has the same S228P and L235E mutations as the inventive antibody displays divergent *in vivo* properties. This illustrates that the *in vitro* properties of an antibody, with respect to Fc receptor activation, is not predictive of activity *in vivo*. By the same token, the skilled artisan could not and would not have generalized from the reports of *in vitro* activity by Erickson-Miller, Holmes, and Taylor to an *a priori* expectation that another antibody with the S228P and L235E mutations, as presently claimed, would display a like activity *in vivo*.

To the contrary, Reddy *et al.* shows and the Takahashi Declaration attests that an ability by a putative therapeutic antibody not to activate the immune response via Fc cross-linking *in vivo* is wholly unpredictable. Yet, as shown in Example 15 and Figure 16 of the specification, the 4D11G4PE antibody does not enhance IL-12 production, an indicator of agonistic activity *in vivo* which likewise is unpredictable, and also delays skin graft rejection (Example 19).

In summary, one of ordinary skill could not have predicted, based on the cited references, that the 4D11G4PE antibody would have the documented activity both *in vitro* and *in vivo*. The evidence of record on point, including the Takahashi Declaration, therefore warrants withdrawal of the pending obviousness rejection.

V. Obviousness-Type Double Patenting (OPD) Rejection

Claims 137-139 are provisionally rejected over claims 1-7 of U.S. application serial No. 11/663,340 ("the '340 Application"). Office Action at 12.

Applicants note, however, that the captioned application has an earlier U.S. filing date than does the '340 application. The captioned application represents the U.S. national stage of PCT/JP04/19750, with an international filing date of December 24, 2004, which is also the effective U.S. filing date. See MPEP § 1893.03(b)[1] and 35 U.S.C. § 363[2]. On the other hand, the '340 application is the national stage of PCT/JP05/17463, with an international and an effective U.S. filing date of September 22, 2005.

When the only rejection in an earlier filed application is an ODP rejection, and the later filed application is rejectable on other grounds, then MPEP § 804 mandates that the Examiner withdraw the rejection in the earlier filed application, allowing it to issue:

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[1] "An international application designating the U.S. has two stages (international and national) with the filing date being the same in both stages. Often the date of entry into the national stage is confused with the filing date. It should be borne in mind that the filing date of the international stage application is also the filing date for the national stage application."

[2] "An international application designating the United States shall have the effect, from its international filing date under Article 11 of the treaty, of a national application for patent regularly filed in the Patent and Trademark Office except as otherwise provided in section 102(e) of this title."

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the *earlier* filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Applicants respectfully request, therefore, that the ODP rejection be held in abeyance until the remaining rejections are overcome. Alternatively, should the Examiner withdraw the remaining rejections, Applicants respectfully request that he also withdraw the ODP rejection and allow the captioned application, pursuant to MPEP § 804.

VI. Potential § 103(a) Rejection in view of US Appl. No. 11/663,340

The Examiner alleges that claims 137-139 are directed to an invention not patentably distinct from claims 1-7 of the '340 Application. Thus, he requests a "showing that the inventions were commonly owned at the time the invention in this application was made [to] preclude a rejection under 35 U.S.C. 103(a)." Office Action at 12.

The '340 Application cannot be the basis of a Section 103(a) rejection, however, because it does not qualify as Section 102(e) art against the captioned application. This is so because PCT/JP05/17463, the international-stage counterpart of the '340 Application, was **not** published in English. See MPEP § 706.02(f)(1)[3].

The requested statement of co-ownership under 35 U.S.C. § 103(c) is necessary only in relation to rejections under Sections 102(f), (g) and (e). In view of the foregoing, therefore, Applicants submit that no such statement is warranted here.

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[3] "(2) If the international application was filed on or after November 29, 2000, but did not designate the United States or was not published in English under PCT Article 21(2), do not treat the international filing date as a U.S. filing date for prior art purposes. In this situation, do not apply the reference as of its international filing date, its date of completion of the 35 U.S.C. 371(c)(1), (2) and (4) requirements, or any earlier filing date to which such an international application claims benefit or priority. The reference may be applied under 35 U.S.C. 102(a) or (b) as of its publication date, or 35 U.S.C. 102(e) as of any later U.S. filing date of an application that properly claimed the benefit of the international application (if applicable)" (emphasis added).

CONCLUSION

Applicants submit that this application is in condition for allowance, and they request an early indication to this effect. Examiner Gambel also is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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